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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,022	10/20/2003	Frank Hallock Ebetino	9071M	4104

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EXAMINER

BERNHARDT, EMILY B

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 03/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	Application No. 10/689,022	Applicant(s) EBETINO ET AL.	
	Examiner Emily Bernhardt	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 39-58 is/are pending in the application.
- 4a) Of the above claim(s) 53-58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 39-42, 45 and 47-49 is/are rejected.
- 7) ☒ Claim(s) 43, 44, 46, 50 and 51 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/10/04 & 7/28/04 & 10/25/04</u> | 6) <input type="checkbox"/> Other: _____ |

Applicants' election of Group III subject matter with traverse in the reply filed 12/15/05 is acknowledged. The examiner initially intended to limit formula (iii) (and (v) which is covered by (iii)) to L as N but will consider the 2 "L" choices now present to be part of the elected invention. The traverse is solely directed to limiting the examination to only elected species should said species be free of prior art. This is not being done. A search for elected species resulted in nothing pertinent in the prior art having the required Q variable as amino coupled with the linking group "N-C(O)" in piperazines claimed herein. Thus the search has been extended to cover remaining embodiments of formula iii present in the newly presented claims.

Note that claims 53-58 are withdrawn pending possible rejoinder upon allowance of compound claims covering scope of the use claims.

Claims 39-42,45,47-49 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. "Oxo" is missing in the formula of main claim 39. This appears to be inadvertent as the claims are indicated to be part of Group III subject matter and

thus the claim will be interpreted as having oxo present on the carbon atom alpha to piperazine ring.

2. Nature of “substituted” present throughout the R variables is of indeterminate scope. Specification describes intended functional groups but the scope is intended to be non-limiting as described on p.10. A similar issue was present in Ex parte Remark 15 USPQ 2d 1498 (at p.1500) in which it was decided that claim language that relied on open-ended language was “vague and uncertain” since it was not clear what else was intended to be covered.

3. When “x” is 0 in claim 39 the “L” links are left with a dangling valence and thus intended scope of resulting compounds is not known. Specification appears to give no guidance.

4. In species claims 47-49 “1-methylcarbamoyl” is recited which is not clear since the 1-designation makes no sense. Is N-methylcarbamoyl being claimed or something else?

Claims 43-44,46-51 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

1. Claim 43 depicts “oxo” in the formula not recited in 39 as discussed in the above 112 rejection . This objection will be moot once claim 39 is corrected.

However R⁸ choice in claim 43 is outside the scope of 39. Note in claim 39 the aromatic rings are **directly** attached to the carbon atom which is attached to the piperazine ring;

2. Claim 44 has the same problem with “oxo” as does 43 but also “Q” choice is outside those covered in claim 39 as well as R⁸ choices;

3. Claim 46 recites species that all contain “oxo” which is missing from claim 39. Also propionamide species are outside the scope of R⁸ . Applicants are also requested to check each species’ scope to determine if other groups present are within the scope of 39;

4. Claims 47-51 all depend on a cancelled claim , namely claim 1 .

Claims 39-42,45 and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1.Starting material sources for the heterocyclic rings covered by the variables CR^{5a}R^{5b} are not seen but are required. Such ring systems are virtually non-limiting

as to size, degree of unsaturation, nature of ring atoms, with further fusion thereon and any additional substituent thereon and also includes more than one occurrence of such rings as the variable "x" can be as large as 12. The same applies to carbocyclic and acyclic groups that can expand to 12 fragments in a given compound. Specification is silent as to the availability of necessary reactants needed to prepare such or if they are commercially available. Note In re Howarth 210 USPQ 689; Ex parte Moersch 104 USPQ 122 for the need to show starting material sources commensurate with the claims' scope.

2.As there are no such representative rings/chain links present 1 to 12 times discussed above that have been made corresponding to the instant scope, there is no reasonable basis for assuming that the myriad of compounds embraced by the all the generic claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note Tsubotani applied below directed to epoxides having entirely unrelated uses. The same applies for the scope of optional substituents permitted on all R variables as described in the specification beginning on p.10. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical

art.

Also note the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the billions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves binding to one or more melanocortin receptors. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved” and physiological activity is generally considered to be unpredictable. See *In re Fisher* 166 USPQ 18. Note Fisher an article published in 2005 discusses structure-sensitivity results in similar compounds just in replacing nature and/or number of substituents on phenyl ring corresponding to instant “R”.

3) Direction or guidance- the compounds made and asserted to bind to MC3 and/or MC4 receptors are not representative of the instant scope but are closer to each other than to remaining scope being always substituted with 4-F on phenyl ring in “R” and having substituents of the type embraced by claims 43 or 44. Rings when present at CR^{5a}R^{5b} are mainly pyrrolidines with fewer examples being azetidine, and pyridine;

4) State of the prior art- The compounds are propionylpiperazine derivatives substituted with a variety of groups at the 1-,2- and 4-positions. While such compounds having the mandatory "L-C(-CR)-C(O)-" fragment are known as evident from the art applied below, they are directed to only a small part of applicants' scope and thus do not evidence the many structural permutations permitted in the instant scope are known in the prior art for the same activity relied on herein;

5) Working examples- No test data has been presented (only description of testing protocols) and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 39-41,45 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fotsch (US'324). Fotsch is applied as of its effective filing date

of 7/25/01 since relevant subject matter is described therein. Fotsch describes similar piperazines that bind to one or more melanocortin receptors. See formula I on p.2 through p.4 for various definitions. While the first compounds appearing on pp.70-71 do not anticipate the instant scope they are obvious variants of that claimed herein for the following reasons. Fotsch describes not only phenyl or pyridylmethyl at the 4-position but also includes as a preferred embodiment benzyl. See p.2, section [0032]. Also while carbons on the piperazine ring are mainly unsubstituted as they are in aforementioned species, Fotsch additionally includes alkyl and alkoxyalkyl among other choices as can be seen on p.4 section [0069]. Fotsch also describes other halos in addition to Cl on phenyl corresponding to instant R. See p.4 section [0065]. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the species pointed out above by replacing exemplified groups with others also preferred and in so doing obtain additional compounds with the expectation that they too will possess one or more uses taught by the applied art in view of the equivalency teachings outlined above.

Claims 39-41 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsubotani (US'853). Tsubotani describes similar compounds to that claimed herein that form an oxirane ring corresponding to $CR^{5a}R^{5b}$ and are

used to treat bone disorders. See example 26 which only differs from claim 39 in lacking a substituent on piperazino carbon(s). H vs 1 or 2 Me groups is not deemed a patentable advance absent evidence of superior, unexpected results. Note In re Wood 199 USPQ 137; In re Lohr 137 USPQ 548; In re Fauque 121 USPQ 425. Additionally, note that Tsubotani teaches substitution at all ring positions of the piperazine ring as can be seen in col.12. Claim 41 is also rejected herein since the phenyl is taught can be optionally substituted with groups including fluorine as described in col.6 and col.8, lines 29-32. Thus it would have been obvious to one skilled in the art at the time the invention was made to modify the closest compound pointed out above by methylating at instant R¹ and optionally modifying the phenyl ring with halo substituents and in so doing obtain additional compounds for the uses taught by the art in view of the close structural similarity and equivalency teaching outlined above outlined above.

Claims 43-44, 46 and 50-51 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

A typo is noted in the 3rd species of claim 51 on p.18. Note “**m**aphthalen”.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



Emily Bernhardt
Primary Examiner
Art Unit 1624